INFORMATION AND COMMUNICATION TECHNOLOGIES (ICTS) FOR BIOBANKING AND ONCOLOGY RESEARCH

Analysis, Support Scenarios and a Case Study

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Abstract: Human Tissue Banks are key for Oncological research and practice. Biobanking processes cross many care departments and have a number of stakeholders, often carrying different objectives: quality assurance and process efficiency are hard to garrison. Key issues in a biobanking project are: dedicated organization, process control, completeness of clinical information on samples, integrated Information and Communication Technologies. Fondazione IRCCS Istituto Nazionale dei Tumori is an oncologic research and treatment institution in Milan (Italy). Our project started in October 2007 aiming at revising the whole tissue collection process (from Surgery to Anatomical pathology assessment, to analysis and storage in the Biobank), developing a clinical biobank management system collecting structured data on cases, and designing an RFId-based system able to track the time- and temperature-sensitive specimens' flow. Now that go-live has begun, technological and - above all - organizational challenges of the project can be discussed in detail. We hope other organizations will appreciate our efforts and are willing to apply a biobanking network as soon as possible.

1 INTRODUCTION

Founded in 1925, the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan (henceforth: INT) is recognized as a Scientific Research and Treatment Institution in Oncology. Over 176 research projects are currently under way, publishing nearly 400 scientific papers each year (IF 2272.32). In 2009 INT cared for about 14,000 inpatients, 10,000 day-hospital admissions, 1 million outpatient treatments, 11,500 surgical operations (including 28 liver transplants). It also inspired the Lombardy Oncology Pathology Network (ROL).

This paper will describe our experience as regards the development of a organizational and ICT solutions for quality assurance, traceability and operation support to biobanking of surgical samples for experimental oncology research, sharing challenges and results of our efforts.

2 EXPECTATIONS AND CHALLENGES IN BIOBANKING

Biosamples – e.g. pathologic and normal tissues, blood, serum, nucleic acids – can play a vital role in research that seeks to find new means of preventing, diagnosing or treating cancer, mainly feeding *in vitro* studies at *in vivo* conditions (e.g. on biomarkers, molecular targets, biomolecular characterization, genomics and proteomics), minimizing research costs for future studies. Quality assurance of sampling and processing activities always worries researchers, e.g. because of possible unknown biases on gene expression after tissue devascularization (Spruessel, 2004). In order to produce clinically valid and comparable results, adequate case records, high-tech machinery, standard sampling and testing procedures (SOPs) are

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paramount (Teodorovic, 2003, Bloom 2003).

We started analyzing the Italian and international biobanking scenario (in Oncology above all), trying to find organizational models and ICT solutions to inspire our project. In general, we observed that biobanks in other countries seem to be more recognized as a valuable asset and institutionalized within organizations. Biobanks are often connected to research centers or universities, e.g. the IARC in Lyon – France (*www.iarc.fr*), the Emory University Hospital's Winship Cancer Institute in Atlanta – GA, USA (*http://winshipcancer.emory.edu*). Moreover, in the majority of Italian cases, biobanking is not an institutionalized process within organizations and conceived as non-core by clinical units. Sample collection is not systematic, most are pathology-oriented, and often considered as own property by physicians.

Further on, we looked for biobank information systems and traceability technologies. The first thing we found, is that DNA, semen, or blood banks, for example, are more used in implementing technologies for sample identification and biobank management than tissue biobanks are. This gap is even more relevant in private-run institutions. Relevant cases of tissue banks show dedicated management systems, integrated with local laboratory equipment, which cover not only filing, but also clinical information of patients and specimens. For example, the biobank management system developed by IBM at Karolinska Institutet in Solna – Sweden (*http://ki.se*) is an excellence case among those studied, also as regards the implementation of syntactic and semantic standards to gather data on clinical cases from the hospital information system to the biobank. In Italy, we found mainly local biobanks, where some cancer centers run their own collections and poor support systems (standalone software, or FileMaker® archive..), which generally handle only storage positions and basic clinical data. As regards traceability, we found that, apart from hand-written information on tubes, there is a basic use of barcode labeling and only few interesting cases of Radio Frequency Identification (RFId). In fact, RFId is being recognized also in the healthcare sector as a useful means to improve process safety and control. Despite the growing number of implementation in patient identification, internal logistics, clinical operations (e.g. transfusion/drug administration traceability – Vilamovska, 2009; School of Management of the Politecnico di Milano 2005-2009), there are still few implementations as regards biobanking: on one hand this process requires quite complex functionalities, on the other hand, a local use of this technology only in the biobank may not prove sustainable compared to barcoding. Major issues are seamless integration within the sampling process from surgery to anatomical pathology and to the biobank, as well as operations at very low temperatures. Istituto Ortopedico Rizzoli in Bologna - Italy (*www.btm.ior.it*) traces bone tissues from the biobank to the operatory theatre, where they get updated with information on implanted patients. Moreover, Paoli-Calmettes Institut in Marseilles – France (*www.institutpaolicalmettes.fr*) and Mayo Clinic in Rochester – MN, USA (*http://cancercenter.mayo.edu/mayo/research/biobank)* experimented in pilots that the use of high tech RFId tags for freeze reading is still a capability to be further developed.

Networking is another main issue, on one hand to support the development of biobanks in smaller institutions, on the other hand to exploit the value of local biological assets joining international research pipelines. In Italy focus is still on the setting up of providers' awareness, while foreign initiatives are getting extensive: Tubafrost (www.tubafrost.org), the Spanish National Tumor Bank Network (*www.cnio.es*), the Wales Cancer Bank (www.walescancerbank.com), EuroBioBank (*www.eurobiobank.org*), the American NCI CaBIG project (*https://cabig.nci.nih.gov*) and the Canadian Tumor Repository Network (*https://www.ctrnet.ca*). These projects follow different models, from the creation of virtual collections to the centralization of biobanking facilities.

Summing up, five key challenges can be identified for present and future biobanking projects:

- Organization: institutionalization of the biobanking process within organizations → process-driven view, internal communication and commitment.
- Quality assurance and process monitoring → SOPs and traceability technologies. In particular, RFId has innovative features like dynamic memory, distance accessibility, bulk identification, embedded sensors.
- Completeness of information on case profiles merging data from clinical subsystems → data coding and system integration implementing semantic and syntactic standards (SNOMED, ICD9-CM, ICD-10, EHR HL7, XML).
- Time-lasting preservation and stability → adequate investments in laboratory instrumentation and storage sites.
- Contributing to research → sample use protocols,

syntactic/semantics, biobanking/pathology networks. Web Rich Internet Applications (RIA) enable sophisticated interfaces as in client/server systems, but with a natural capability of supporting networking and cooperation with external organizations.

These subjects will now be addressed presenting the real case of the Oncologic Tissue Bank at INT.

3 TISSUE BIOBANKING AT INT: KEY ISSUES AND RESULTS

The project at the Italian National Cancer Institute in Milan started in 2007 when the Experimental Oncology Dept. discussed with the Chief Information Officer (CIO) the opportunities of ICT support for the local tissue biobank. The ICT Unit and partner Fondazione Politecnico di Milano started investigating processes, staff organization and existing tools, highlighting critical points and needs. Analysis highlighted a situation coherent with the scenario discussed in Section 2: highly fragmented way of working with poor support for activities and low overall effectiveness (uncertain quality assurance, high number of uncollected cases…). Thus, a new targeted project was set up in order to:

- Establish a real biobanking infrastructure;
- Investigate quality control procedures for tissue processing and storing and review the organization implementing a clearly structured biobanking process;
- Ensure the exact identification of specimens;
- Guarantee traceability of operations and transport lead times, monitoring specimens' environmental conditions;
- Automate information flows between Depts.;
- Develop a shared scientific data-base integrated with the hospital information system, where to gather significant clinical information on patients and data on specimens, to support diagnosis and research.

A first help was in 2009 the opening of the Amadeo-Lab, a new seat to concentrate research units and labs, centralizing storage in a dedicated infrastructure. Before, freezers were dispersed among the 9 floors of the INT main building.

The solution we designed is mainly based on a new Tissue Bank information system and the extension of the INT RFId platform to support the entire biobanking workflow (from surgery to freeze). This is represented in Figure 1 (see numbers in brackets). Inpatients at INT are always assigned an RFId wristband at admission, where an accompanying nurse stores information for its unique identification [ref. 1]. This as INT is running an own RFId traceability platform developed for patient/staff identification, access management, treatments safety and so on (Locatelli, 2010). Operating Rooms daily schedule and real time status are broadcasted via HL7 messages, so that technicians in the biobank can plan activities and signal surgeons which cases have a higher relevance. Staff in the O.R. [1] checks-in the patient, verifying its wristband vs. the room planning and their sheets in the clinical system. During surgery [2], samples of tumor or sane tissue are taken for diagnosis. Staff can register and RFId-label sampled specimens on the surgery system (e.g. site of sampling, information for pathologists, notes for the Tissue Bank..) while filling the digital surgery report on the O.R. laptop. Samples are now ready to be sent to the Anatomical Pathology labs: a clerk takes them out and checks them in on the "Tissue Express" [3, 4], a trolley with a plain RFId antenna and tablet PC running a touch-screen software, where to declare which new samples loaded and by whom (each staff member has an RFId badge to log in to systems). Dedicated staff deliver the trolley to the pathology labs and check them in, while it tracks lead times and surrounding temperatures thanks to a RFId semi-active tag installed in the box containing the samples. The software on the tablet PC collects its transmission and joins them with data on carried samples. These are checked in by pathologists reading their labels on their laboratory system [5]. Once they have assessed a sample (macro-, micro-, diagnosis), parts of it are given to a Tissue Bank technician, who identifies it again reading the original RFId label printed in the O.R [5]. The received sample is recorded into the new Tissue Bank information system. Alerts are shown in case processing times or temperatures crossed preset thresholds. The technician proceeds subdividing the sample into aliquots and stocking them into vials, each one labeled with a unique identifier and key data printed into a Datamatrix 2D barcode. After examinations and documentation on the system, aliquots are frozen in the laboratory and periodically transferred to the new biolab [6, 7].

The Tissue Bank information system routinely collects relevant process and clinical data via HL7 and Web Services integration from the O.R. system, the Anatomical Pathology, the slides digitalizer, the

RFId platform, the Enterprise Patient Registry, the Enterprise Clinical and Reports Repository, and from external documentation. All relevant data is linked to the tissue collection and organized enabling the user to browse collections per sample-, patient-, or clinical data. The system manages storage and sample retrieval, offering research and browsing capabilities through rooms, freezers and boxes containing samples, supporting technicians in withdrawing cases and aliquots for research.

In our context, as probably in many other research institutions, the biggest challenge we had to face was to standardize sample-related data collected in two heterogeneous historical databases: an experimental stand-alone application for breast and ovarian cancer cases and a MSExcel® archive for other kind of samples. Basic data on samples was written down on paper during handling and then entered manually. No integrated system could ever have been implemented with such a data structure. The review took almost a year and required a tight collaboration between the ICT Unit and clinical staff. As results we obtained a common data structure to be implemented, thus recovering all historical collections. The new database was designed to be more flexible and general as possible, thus being able in the future to extend the institutional biobank to other types of biological material (e.g. blood, RNA, tissue microarray), and also to join networks. The Tissue Bank information system has been designed as a web-based Rich Internet Application, allowing a very complete and friendly user interface. Moreover, the three-tier application architecture will enable us to easily scale the system, simplifying maintenance and evolution (data and application server are centralized, while users access the latest version of the application via web browser).

4 DISCUSSION: TECHNOLOGY-RELATED AND ORGANIZATIONAL OPEN ISSUES

The solution has been available to users in Experimental Oncology Labs since May 2010 for user testing. Go live was October 2010, starting from the Urology and Melanoma-Sarcoma Operating Room, reaching full coverage of 10 ORs at INT by Spring 2011.

To ease organizational change, we involved key actors and final users in analysis and design phases: since the beginning we engaged Operating Theater, Anatomical Pathology and Tissue Bank referees in order to approach the process from a global point of view. Decision makers and operative referees were committed to analyze processes, IT support, documentation and information flows, critical aspects, considering all points of view. Once As-Is analyses were shared in focused meetings, discus-

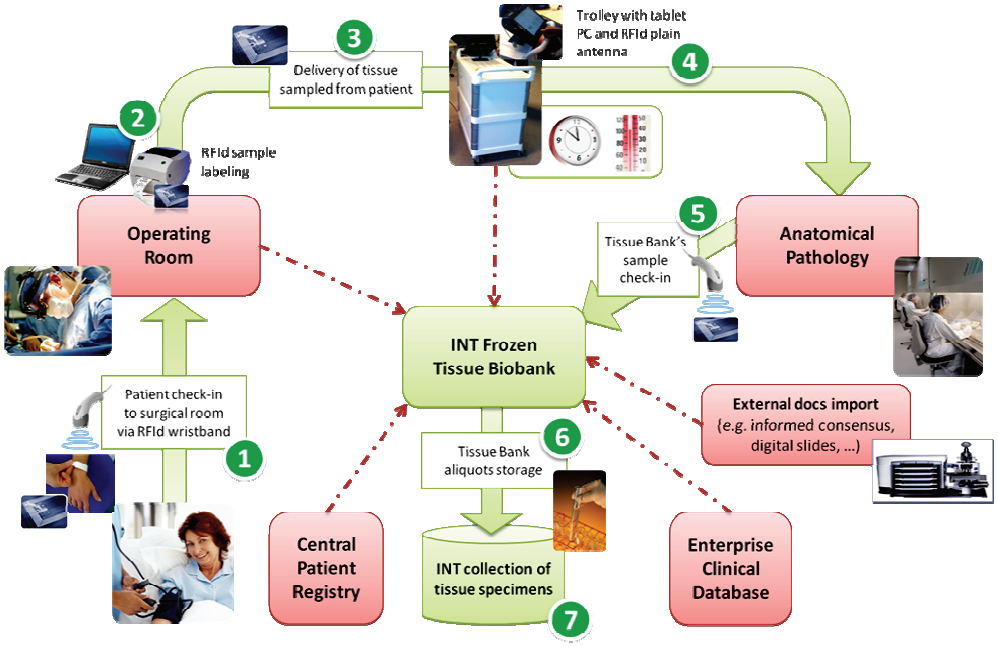

Figure 1: Schema of the process and ICT solution supporting the new Tissue Bank at INT.

sion followed on hypothesis about new ICT solutions and process reengineering. Several meetings were necessary to address issues like: what type and how to use RFId, how to integrate the new Tissue Bank system to the different Hospital Information System (HIS) modules involved in the biobanking process, which would be the tracking steps in delivering samples, how to modify surgical workflow in taking and recording tissue samples, and so on. After defining specifications, we had to coordinate all technology partners, one for each system involved in the biobanking process. This required a huge effort, to reconcile views and garrison system integration.

Change management and implementation activities have been running for almost a year, while consensus building efforts accompanied the project from the beginning. In fact, change management issues were challenging, because of some peculiarities common to many healthcare projects. First of all, a process like biobanking crosses at least three different care departments and has a number of other stakeholders (Anesthetists, Auxiliary Personnel, the Scientific Directorate, the Ethics Office...), often carrying different priorities and views of the process. Common to contexts like public institutions were a certain resistance to change while introducing a process-driven way of thinking (instead of focusing on own clinical areas), and a general low computer literacy. Internal project management at INT was undertaken by the CIO (as usually happens here for ICT projects, the ICT Office takes leadership), with strong internal commitment by INT top management. The CIO was supported by a direct delegate and colleagues from Fondazione Politecnico di Milano. Strong support was required from the clinical area, so that clinical-scientific issues could be taken into consideration during design. The existence of previous successful projects (e.g. RFId transfusion traceability, new Surgery management system...) involving the same roles and their referees helped to boost cooperation.

4.1 RFId Maturity – Can Healthcare Organizations Face this Alone?

Positive experiences on using HF13,56 MHz RFId technology for patient, operator and item identification with near field applications (e.g. in the transfusion chain) led us to extend the use of this technology also to biobanking. We searched the market for RFId solutions ready for biobanking, but the only one meeting our needs was focused on vials identification, too expensive, and from outside Italy (with potential difficulties in customization and integration activities). So, we evaluated how to develop the extension on our own.

First of all, we learned RFId is not at all an "on-the-shelf" technology. Even being supported by a high-profile partner, many solutions had to be found in an experimental way. Variety in implementation of interoperability and communication standards by producers of tags and devices, hardness to find mature RFId handheld readers, unexpected behaviour of devices and drivers instability, are some of the main challenges to be faced. In fact, also because of low experienced suppliers, we had to work by a trial-and-error approach, often re-designing integration components. This slowed up system developments substantially.

Two key examples will help understanding this issue. First, the trolley had to be designed and produced with craftsmanship, while unexpected interactions of the electromagnetic field with samples required many modifications to obtain a field with required characteristics such as shape and strength. The second example comes from a request by researchers to prove that RFId would not damage samples. Once we started assessing literature (among which: ICNIRP, 1998; Ahlbom, 2004; Jauchem, 2008), we discovered that RFId technology isn't supported by a consolidated environment due to lack of specific laws and implementation guidelines for the healthcare sector: studies on long-term consequences of biological interactions connected to HF RFId fields have not led to conclusive result yet. What we concluded after scrutinizing a large number of papers, is that, given the physical characteristics of tissues and the type of RFId emissions used (short impulses, frequency, power of few dozen mW), both short- and long-term effects on tissues can be negligible. Besides, we verified through several tests that the use of RFId would not interfere with ordinary clinical activities (Radiology, Radiotherapy..) and medical equipment. Only tests done on infusion pumps led to a 5-10 cm minimum distance requirement in RFId operations, due to slight alteration in measured volumes in case of repeated read/write activities.

Another issue was transport temperature monitoring via semi-active or active tags: scouting to find the right device with proper reliability and battery duration was hard.

But the main critical point in using RFId for biobanking is represented by extreme low storage temperatures. Starting from -80°C of mechanic freezers, tissues can be stocked in liquid nitrogen at -196°C: standard RFId tags are not readable under -30/-40°C. Specific extremely expensive RFId solutions (vials with little ad-hoc button-size tags) can improve reliability when sample is defrosted,

but with no significant enhancements for readability. This were the main reasons why we decided – for now- to switch to barcode for supporting sample identification at storage and retrieval, relying on 2D Datamatrix labels to code more data on each vial.

4.2 Expected Improvements

Technicians experience a remarkable rise in number and quality of surgical specimens provided by the operating theatre to the bank: before the bank was able to collect specimens from less than 40% of surgeries, often not knowing certain data about how they have been processed before. State-of-the-art facilities and tools will allow a more accurate screening of incoming tissue samples, better support high level research activities, and even to offer its services (both storage space and sample provision) to external organizations.

5 CONCLUSIONS

In 2007-2010 INT redesigned biobanking processes from the operating theatre to storage, developing a new Biobank Management System conceived as a collector of all information flows about patients and samples coming from clinical subsystems (Surgery, Anatomical pathology, Laboratory...). This was also integrated with the enterprise RFId platform to identify samples, register process and transport lead times, and to monitor specimens' processing thanks to readers at key steps of the process and trays tracing environmental conditions on samples leaving the operatory theatre. Systems are supporting information flows all over processes, creating links between applications and units that were not cooperating at best and enabling process control and quality, with an expected impact also on research. The biobank management system was designed as a flexible structure, and a web-based application able to manage different biobanks and collections into a virtual repository, the main feature of a network. A first initiative of shared infrastructure has just started with partner hospitals from a Regional research group on Colon-Recto Cancer. Moreover, INT is now trying to develop an extranet module and align its systems to international guidelines in order to apply international biobank networks (BBMRI...) and offer its services to other institutions.

Challenges to be faced are very high. Innovation in Public Healthcare meets a lot of difficulties in being adopted due to strong organizational habits and rules, as well as low computer literacy; rising staff commitment towards a project/process involving many different departments is a daily commitment. Thus, change management issues and accurate process redesign activities are key to success. Introduction of innovation in such contexts must be gradual (pilot projects), proceeding by further refining and upgrades of systems. Challenges were also technology-related. We realized that RFId technology is not at all an "on-the-shelf" technology and its implementation is not supported by a mature environment due to lack of specific laws and guidelines for the healthcare sector; this required experimenting solutions and developing technology skills on our own together with partners.

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